IL-17–high asthma with features of a psoriasis immunophenotype

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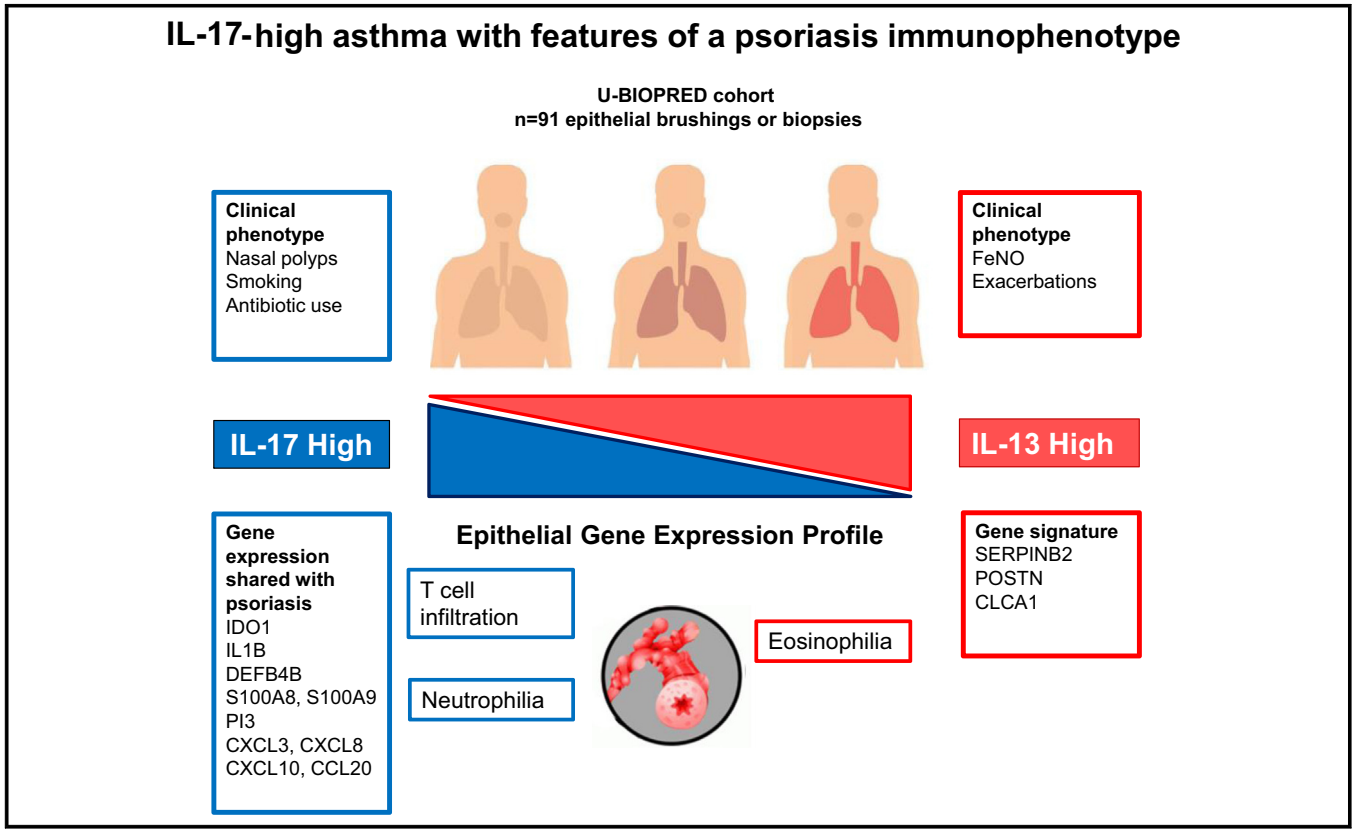
GRAPHICAL ABSTRACT



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Background: The role of IL-17 immunity is well established in patients with inflammatory diseases, such as psoriasis and inflammatory bowel disease, but not in asthmatic patients, in whom further study is required.

Objective: We sought to undertake a deep phenotyping study of asthmatic patients with upregulated IL-17 immunity.

Methods: Whole-genome transcriptomic analysis was performed by using epithelial brushings, bronchial biopsy specimens (91 asthmatic patients and 46 healthy control subjects), and whole blood samples (n = 498) from the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort. Gene signatures induced *in vitro* by IL-17 and IL-13 in bronchial epithelial cells were used to identify patients with IL-17–high and IL-13–high asthma phenotypes.

Results: Twenty-two of 91 patients were identified with IL-17, and 9 patients were identified with IL-13 gene signatures. The patients with IL-17–high asthma were characterized by risk of frequent exacerbations, airway (sputum and mucosal) neutrophilia, decreased lung microbiota diversity, and urinary biomarker evidence of activation of the thromboxane B2 pathway. In pathway analysis the differentially expressed genes in patients with IL-17-high asthma were shared with those reported as altered in psoriasis lesions and included genes regulating epithelial barrier function and defense mechanisms, such as *IL1B*, *IL6*, *IL8*, and β-defensin.

Conclusion: The IL-17–high asthma phenotype, characterized by bronchial epithelial dysfunction and upregulated antimicrobial and inflammatory response, resembles the immunophenotype of psoriasis, including activation of the thromboxane B2 pathway, which should be considered a biomarker for this phenotype in further studies, including clinical trials targeting IL-17. (J Allergy Clin Immunol 2019;144:1198-213.)

Key words: *IL-17, asthma, bronchial biopsies, bronchial brushings, biomarkers, psoriasis*

Abbreviations used

BC:	Cluster derived from transcriptomic data in whole blood
DEG:	Differentially expressed gene
DPP4:	Dipeptidyl peptidase 4
FENO:	Fraction of exhaled nitric oxide
ICS:	Inhaled corticosteroid
IPA:	Ingenuity Pathway Analysis
NGS:	Next-generation sequencing
TDA:	Topological data analysis
U-BIOPRED:	Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Asthma presents in variable clinical forms that can be stratified into multiple clinical phenotypes driven by distinct pathologic mechanisms that define so-called asthma endotypes.[1,2] This stratified approach to asthma is useful for both advancing the understanding disease pathogenesis and optimizing treatment with inhaled corticosteroids (ICSs)[3,4] and biologics.[5,6] The type 2 (T2) interleukins IL-4, IL-5, and IL-13 are pivotal in asthmatic patients, driving the isotype switch to IgE production, eosinophilia, mast cell activation, and airways remodeling.[7] Trials with T2 biologics have shown that T2 cytokines play key roles in a significant proportion of asthmatic patients, particularly those with prominent eosinophilic inflammation.[8] However, substantial numbers of patients do not respond to T2 biologics,[9] suggesting the presence of T2-independent mechanisms.

The role of IL-17 in asthma is unclear. IL-17 immunity has been associated with asthma exacerbations,[10,11] but it is not understood whether it is a driver of an asthma phenotype or a marker of mucosal defense responses to microbial stimulus. In a study of 51 asthmatic patients with a range of clinical severities, Choy et al[12] identified a group characterized by high expression of genes in the bronchial epithelium demonstrated to be upregulated *in vitro* by IL-17A.[12] In these patients epithelial T17 and T2 gene signatures were inversely correlated, suggesting they are mutually exclusive. IL-17 is produced by T17 cells, γδ T cells, and innate cells, such as type 3 innate lymphoid cells, natural killer cells, and natural killer T cells.[13] The IL-17 family consists of 6 members, with antimicrobial activity associated mainly with IL-17A, IL-17F, and IL-17A/F heterodimer members.[14] IL-17 is coregulated by the transcription factor retinoid-related orphan receptor γt, and activation of IL-17 or IL-22 receptors expressed on bronchial epithelial cells induces neutrophil chemotactic factors, such as GM-CSF and CXCL8; cytokines, such as IL-6; and the antimicrobial peptides β-defensins and S100 proteins.[15]

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The aim of this study was to advance the understanding of the clinical features and molecular mechanisms of asthmatic patients characterized by upregulation of IL-17. We used the large transcriptomics and clinical data sets from the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) study and stratified patients according to epithelial and mucosal expression of IL-13 and IL-17 gene signatures described by Woodruff et al[16] and Choy et al,[12] respectively. Because IL-17 secretion is not limited to T cells and we do not know the source of these cytokines modulating the lung epithelium, we used the definition of IL-17 instead of the T17 gene signature. Systemic activation of IL-17 immunity was assessed in blood by analyzing the transcriptomic data set derived from whole blood microarray analysis. We applied cluster analysis to the bronchial and blood transcriptomic data sets and compared the identified groups with respect to the clinical characteristics that define asthma severity, namely levels of symptoms and frequencies of exacerbations, and looked for biomarkers in blood and urine in the large U-BIOPRED data set of serum proteins and urinary eicosanoids.

METHODS

Study design and methods

The design, participants, and sample collection methods in the U-BIOPRED study, engaging 16 clinical centers in 11 European countries, have been published.[17] The study was approved by the ethics committee for each participating clinical institution (registered on ClinicalTrials.gov: NCT01982162). All participants provided written informed consent.

Patients with severe asthma had uncontrolled symptoms defined by the Global Initiative for Asthma guidelines and/or frequent exacerbations (>2 per year) despite high-dose ICSs (≥1000 μg/d of fluticasone propionate or equivalent dose of other ICS) and were under follow-up by a respiratory physician for at least 6 months before enrollment to optimize asthma control and assess medication adherence (see Table E1 in this article's Online Repository at www.jacionline.org). Patients with mild-to-moderate asthma had controlled or partially controlled symptoms (defined by Global Initiative for Asthma guidelines) while receiving treatment with less than 500 μg/d fluticasone propionate or equivalent (see Table E1). Healthy control subjects had no history of asthma, wheeze, or other chronic respiratory disease, and prebronchodilator FEV_1 was 80% of predicted value or greater.

All participants underwent spirometry, fraction of exhaled nitric oxide (F_{ENO}) measurement, sputum induction,[18] and assessment for atopy. Whole blood samples from 246 nonsmoking patients with severe asthma, 88 smoking patients with severe asthma, 77 nonsmoking patients with mild-to-moderate asthma, and 87 healthy nonsmokers underwent transcriptomic analysis, and urine samples were collected for lipid mediator measurement. Bronchial brushings and biopsies were performed in 91 asthmatic patients with severe or mild-to-moderate asthma; all were nonsmokers for more than 12 months, with a less than 5 pack-year history. Biopsy specimens were processed for immunohistochemistry.

Biopsy specimens, brushings, and whole blood samples were analyzed for whole-genome expression by using the HT HG-U133+ PM microarray platform (Affymetrix Plus 2.0; Affymetrix, Santa Clara, Calif), as previously described.[19] Sputum samples were also subjected to 16S rRNA sequencing and next-generation sequencing–based metagenomic analysis.

Statistical analysis

Gene expression data were analyzed by using general linear model–based statistical tests, and hierarchical clustering of transcriptomics data was performed by using the average linkage and Euclidean metric methods with each variable normalized to mean 0 and variance by using Qlucore Omics Explorer 3.3 software (Qlucore, Lund, Sweden). Clinical variables and biomarker data were compared by using Kruskal-Wallis tests with Spotfire 7.0.2. Correlations were tested with Spearman r statistics. Gene expression data from blood were analyzed by using topological data analysis (TDA) performed in Ayasdi Core software (Ayasdi, Menlo Park, Calif).[11,20,21] Function and pathway enrichment analysis were performed with the Ingenuity Pathway Analysis (IPA) package. Unless otherwise stated, clinical data were considered significant at a P value of less than .05. For global unbiased analysis of omics data, Benjamini-Hochberg multiple correction for the rate of false-positive responses was applied.

For more details on the methods used in this study, see the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

Gene expression in the epithelium

Hierarchical clustering based on IL-13 and IL-17 gene signatures defines 3 asthma groups. A total of 85 brushings and 68 bronchial biopsy specimens with high-quality RNA were obtained from 91 participants; although some participants provided both sample types, for some participants, only 1 sample type was obtained or yielded good quality RNA. Hierarchical clustering using IL-13 and IL-17 gene signatures applied separately to data from brushings and biopsy specimens revealed in total 10 patients with an IL-13–high phenotype and 22 asthmatic patients with an IL-17–high phenotype (Fig 1, *A* and *B*, and see Table E2 in this article's Online Repository at www.jacionline.org). One participant had simultaneously high expression of both the IL-13–high and IL-17–high phenotypes (Fig 1, *A* and *B*), and none of the others had simultaneous high expression of both IL-13 and IL-17 gene signatures. Thus IL-17 and IL-13 gene expression scores correlated negatively (rho = −0.646, $P < .0001$; Fig 1, *D*). Sixty participants did not show either the IL-13 or IL-17 gene signatures and were defined accordingly as of the IL-13/IL-17–low phenotype, indicating that their lung cytokine environment might be less polarized.

Additional clustering performed with the combined set of 8 genes from the IL-13 and IL-17 signatures confirmed distinct IL-13–high (n = 13) and IL-17–high (n = 13) clusters, with no clear cluster of patients with simultaneously high expression of both signatures (Fig 1, *C*). These clusters consisted largely of the same subjects identified by means of hierarchical clustering using separate gene signatures.

Differentially expressed genes in the epithelium in the IL-17–high group reveals dysregulation of epithelial barrier mechanisms. A complete list of differentially expressed genes (DEGs) in brushings from patients with IL-17–high asthma was generated by excluding mRNAs differentially expressed in the comparison between patients with IL-13–high asthma (n = 9) and healthy participants (n = 64, $P < .05$) from the list of genes differentially expressed when comparing patients with IL-17–high asthma (n = 22) and all other participants (comprising those with IL-13–high asthma [n = 9], those with IL-13/IL-17–low asthma [n = 54] and healthy participants [n = 64, $q < .05$]). Comparison with all other participants identified 797 DEGs either overexpressed or underexpressed in the IL-17–high group with a q value of less than 0.05 (for a complete list of DEGs, see Table E3 in this article's Online Repository at www.jacionline.org), including the host defense genes *CCL20* ($q = 0.0004$), *IL1B* ($q = 0.0009$), *IL6* ($q = 0.0003$), *IL8* ($q = 0.0003$), *TL2R* ($q = 0.00013$), β-defensin ($q = 0.00065$), *S100A8* ($q = 0.0009$), *S100A9* ($q = 0.0006$), and *ICAM1* ($q = 0.0003$), many of which, (eg, *CCL20*, *IL1B*, β-defensin,

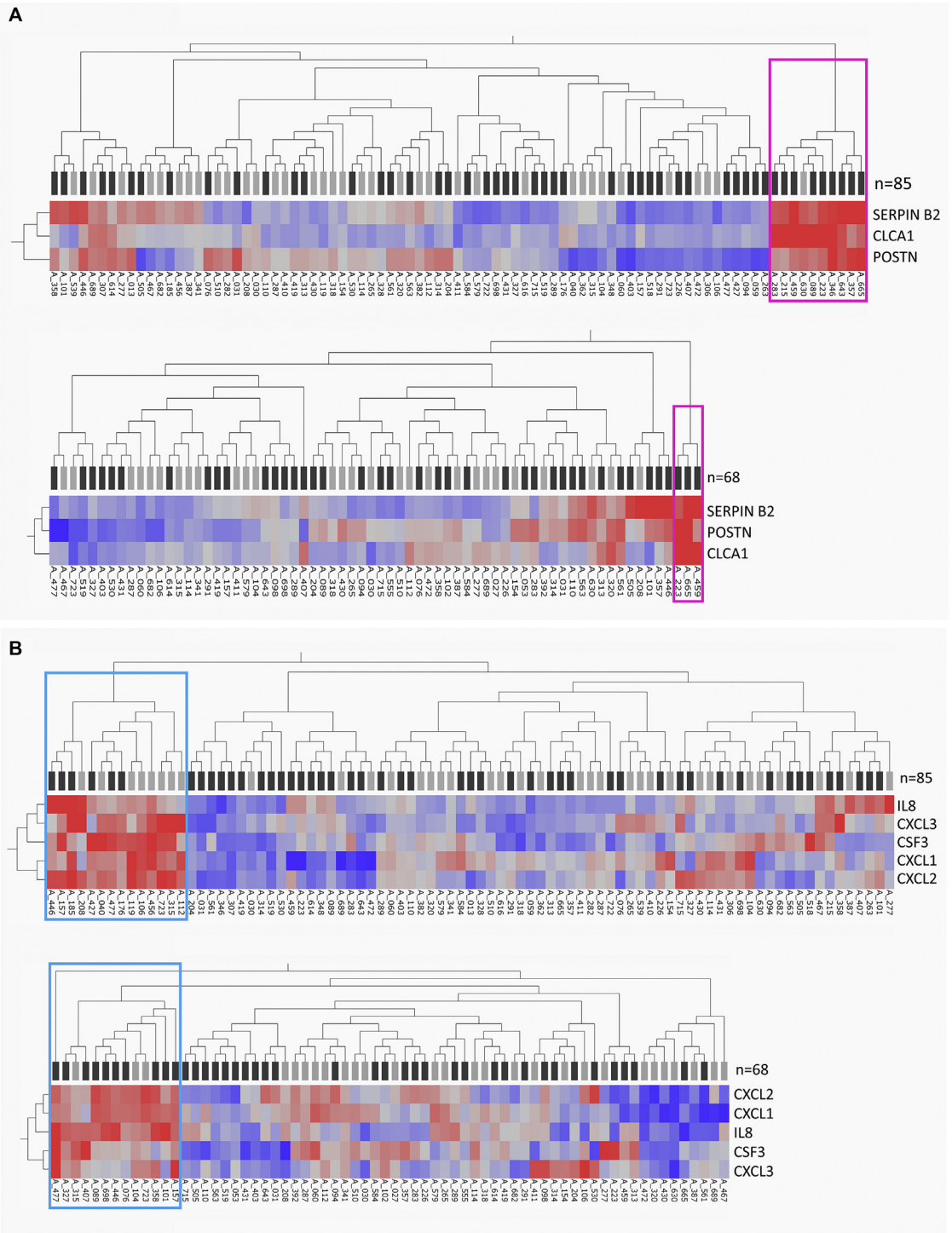

FIG 1. IL-13–high and IL-17–high clusters in the U-BIOPRED asthma cohort. Heat maps show clusters based on gene expression data from 85 brushings and 68 biopsy specimens from 91 asthmatic patients: mild-to-moderate *(gray bars)* and severe *(black bars)* asthma. The IL-13–high and IL-17–high clusters are delineated by *pink* and *turquoise boxes*, respectively. **A,** IL-13–high cluster based on the IL-13 gene signature (*POSTN*, *CLCA1*, and *SERPINB2*) in bronchial brushings (*top*, n = 10) and biopsy specimens (*bottom*, n = 3). **B,** IL-17–high cluster based on the IL-17 gene signature (*CSF3, CXCL1, CXCL2, CXCL3,* and *CXCL8* [IL-8]) in bronchial brushings (*top*, n = 14) and bronchial biopsy specimens (*bottom*, n = 13). **C,** Hierarchical clustering of IL-13–high and IL-17–high clusters based on expression levels of the combined IL-17– and IL-13–regulated genes in bronchial brushings. Euclidean distance, average linkage, and color scale are presented as $\log_2$ fold changes, with a range from −2.0 (blue) through 0.0 (gray) to +2.0 (red). Data from multiple probes were collapsed to single genes by using the highest value. Sample IDs are indicated on the *x-axis*. **D,** Correlation between *IL13* and *IL17* gene signature scores. Gene expression scores were calculated from normalized and zero-centered gene expression values. Spearman correlation and 2-tailed *P* values are shown.

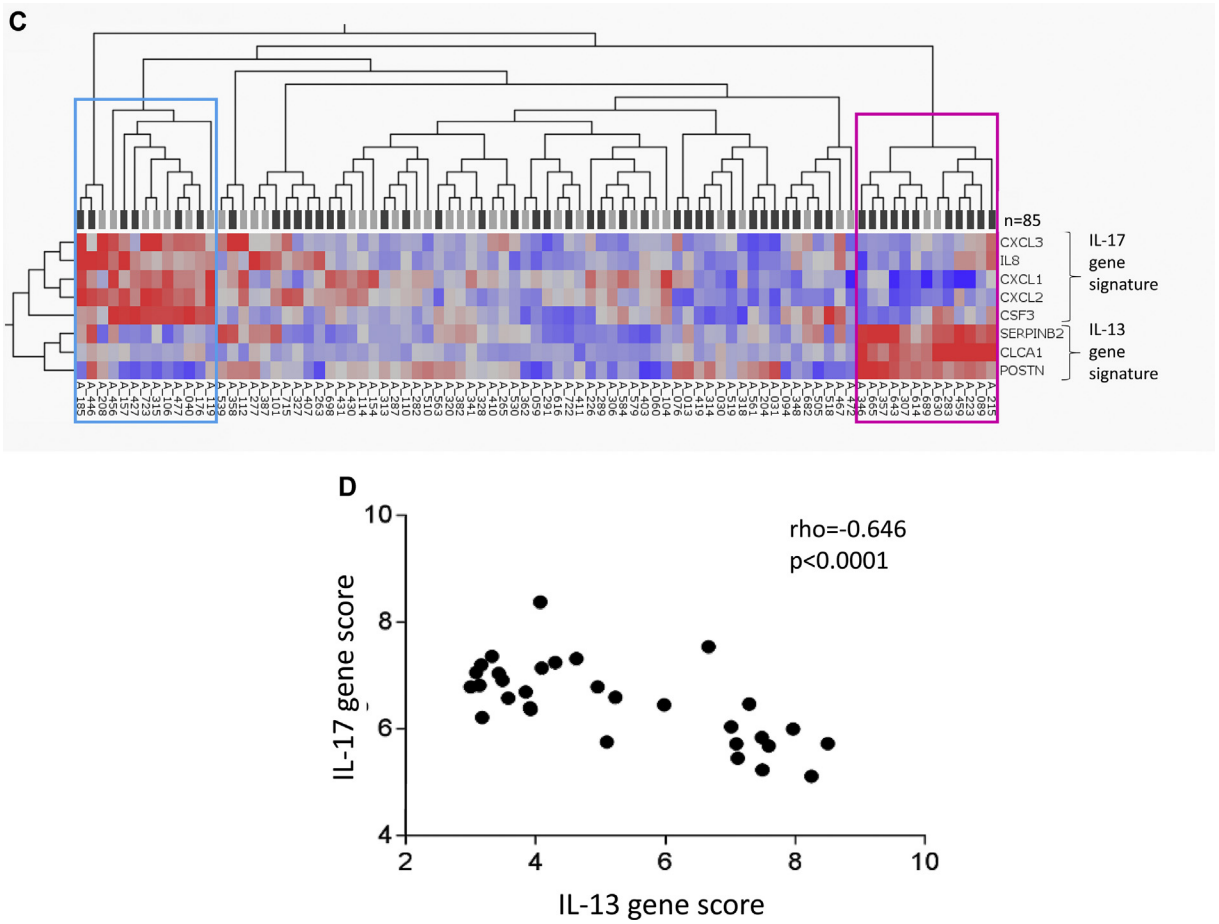

FIG 1. *Continued.*

IL6, and *IL8*) are associated with T17 pathway activation.[22,23] IPA regulator effects analysis restricted to immune, infection, and inflammatory disease identified IL-17A as the regulator with the highest consistency score (Table I).

Expression of RAR-related orphan receptor C *(RORC)*, the gene for the nuclear receptor retinoid-related orphan receptor γ, a regulator of IL-17 and IL-22, was decreased in the IL-17–high group ($q < 0.003$), which is possibly a sign of negative transcriptional regulation. Other host defense DEGs included *SAA4* and *TREM1* ($q = 0.0004$ and 0.0008, respectively) and genes for StAR-related lipid transfer domain protein 7 *(STARD7)* and *IL33*, an alarmin cytokine with a crucial role in innate immunity, inflammation, and T2 responses.[24] Expression of several key tight junction genes was also significantly lower (*CLDN1* [$q = 0.0004$], *CLDN8*, *OCLN*, and *CTNNB1* [$q = 0.0021$]).

IL-17–high phenotype–associated DEGs overlap with dysregulated genes in patients with psoriasis. Canonical pathway analysis identified "role of IL-17 in psoriasis" as the pathway with the greatest overlap with the list of 797 DEGs ($q = 3.6E-04$, Table II), which is supported by disease and function enrichment analysis, identifying 79 genes previously implicated in patients with psoriasis ($P = 5.32E-17$, see Table E4 in this article's Online Repository at www.jacionline.org). One hundred seventy of 797 IL-17–high genes mapped to the 3388 psoriasis genes previously published (Fig 2).[22,25] Genes overexpressed in bronchial epithelial cells of patients with IL-17–high asthma (Fig 2, *C*) tended to belong to the genes overexpressed in psoriasis lesions (Fig 2, *A*) and normalized by treatment of psoriasis with the mAb against IL-17 receptor A, brodalumab.[25] Genes underexpressed in bronchial epithelial cells in the participants with IL-17–high asthma tended to belong to genes underexpressed in patients with psoriasis and normalized by brodalumab (Fig 2, *B*).[25]

Epithelial transcripts for dipeptidyl peptidase 4 *(DPP4)* were significantly lower in the group with IL-17–high asthma (see Fig E1 in this article's Online Repository at www.jacionline.org), a surprising finding given the efficacy of *DPP4* inhibition as a treatment for psoriasis.[26] Furthermore, *DPP4* transcripts were greater in the group with IL-13–high asthma when compared with the group with IL-17–high asthma, pointing to reciprocal expression of *DPP4* in the 2 phenotypes. Consistent with a potential value of *DPP4* expression as a biomarker, similar differences were seen for serum DPP-4 protein levels (data not shown).

Clinical and pathobiological features of the epithelial IL-17–high group

Fifty-nine percent of patients with IL-17–high asthma had severe disease (89% in the IL-13–high and 53% in the IL-13/IL-17–low groups); 38% had more than 2 asthma exacerbations in the preceding year, which was greater than in the IL-13/IL-17–

TABLE I. IPA regulator effects networks that map to the list of 797 DEGs (IL-17–high vs all other participants, $q < 0.05$)

Regulators	Consistency score*	Target molecules in data set	Diseases and functions
IL17A	8.85	CCL20, CD14, CSF3, CXCL3, CXCL8, DEFB4A/DEFB4B, ICAM1, IL1B, IL6, PTGS2	Adhesion of immune cells, binding of professional phagocytic cells, inflammatory response, leukocyte migration, response of phagocytes
TLR1	8.66	CXCL8, IL1B, IL6	Adhesion of immune cells, cell movement of leukocytes, immune response of cells, inflammatory response, replication of HIV-1
IL18	7.67	CCL4, CXCL10, CXCL11, CXCL8, CXCL9, ICAM1, IL1B, IL6, PTGS2	Cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
TLR7	7.24	CCL20, CCL4, CXCL10, CXCL3, CXCL8, CXCL9, ICAM1, IL1B, IL6, MYD88, PLAU	Activation of dendritic cells, inflammatory response, leukocyte migration
TBK1	7.16	CXCL10, CXCL11, CXCL8, IL6, IRF7	Cell movement of leukocytes, immune response of cells, inflammatory response, migration of lymphatic system cells
TNF	6.95	CCL20, CCL4, CXCL10, CXCL11, CXCL3, CXCL8, CXCL9, DEFB4A/DEFB4B, ICAM1, IL1B, PLAU, S100A8, S100A9, TLR2	Adhesion of phagocytes, cell movement of granulocytes, cell movement of T lymphocytes
FOXO1	6.71	CCL20, CXCL10, CXCL8, DEFB4A/DEFB4B, IL6	Cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
IFNL1	6.71	CXCL10, CXCL11, CXCL8, CXCL9, IL6	Cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
TLR9	6.71	CCL4, CXCL10, CXCL8, CXCL9, IL6	Cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
CSF2	6.12	CCR1, CXCL8, ICAM1, IL1B, IL6, TLR2	Binding of professional phagocytic cells, cell movement of neutrophils, migration of lymphatic system cells, replication of HIV-1
FOXO3	6.00	CXCL10, CXCL8, DEFB4A/DEFB4B, IL6	Cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
FCER1	6.00	CCL4, CXCL8, IL1B, IL6	Adhesion of immune cells, cell movement of leukocytes, inflammatory response
EZH2	5.31	BIRC3, CSF3, CXCL10, CXCL11, CXCL8, IL6	Immune response of cells, migration of lymphatic system cells, response of phagocytes
CAMP	5.30	CCL20, CCL4, CXCL10, CXCL8, FPR2, IL1B, IL6, TLR2	Cell movement of granulocytes, immune response of cells, migration of lymphatic system cells
ADORA3	5.20	CCL4, CXCL3, CXCL8	Cell movement of mononuclear leukocytes, cell movement of neutrophils, chemotaxis of leukocytes
TICAM1	5.20	CXCL10, CXCL11, CXCL8	Chemotaxis of leukocytes, migration of lymphatic system cells, migration of mononuclear leukocytes
CD40LG	4.47	CCL20, CXCL8, ICAM1, IL1B, IL6	Adhesion of immune cells, cell movement of leukocytes
IKBKB	4.47	CCL4, CXCL8, ICAM1, IL1B, IL6	Adhesion of immune cells, cell movement of leukocytes
IRF4	4.47	CCL20, CXCL10, CXCL11, CXCL3, CXCL9	Cell movement of mononuclear leukocytes, chemotaxis of leukocytes
CCL5	4.08	ADGRE5, CCL4, CCR1, CXCL8, IL1B, IL6	Adhesion of immune cells, cell movement of leukocytes
ERK	4.00	CCL4, CXCL10, CXCL8, ICAM1	Migration of lymphatic system cells, migration of mononuclear leukocytes

*The consistency score is a measure of the causal consistency and dense connection of a regulator effects network. Analysis was applied to the 797 DEGs unique for the IL-17–high group and was restricted to the following search items: immune, infection, and inflammatory diseases.

low group (15%, $P = .025$) but not different from the IL-13–high group (44%, Table III). Patients with IL-17–high asthma had increased occurrence (43%) of nasal polyps and more significant smoking history, and 27% had been receiving regular antibiotics but similar maintenance oral corticosteroid treatment when compared with the other groups.

Consistent with the role of IL-13 in patients with eosinophilic inflammation, the IL-13–high group had increased serum IL-13 levels (mean, 2.15 pg/mL), sputum and blood eosinophil counts (49.3% and 7.9%, respectively; Fig 3), and FENO and serum periostin values (Table III). In contrast, the IL-17–high phenotype had greater airways neutrophilia both in sputum and the bronchial submucosa (Fig 3 and Table III). Immunohistologic staining of bronchial biopsy specimens showed increased submucosal T-cell ($CD3^+$ and $CD4^+$) and lower mast cell counts in the IL-17–high group compared with the IL-13/IL-17–low group but not when compared with the IL-13–high group (Fig 4).

Gene expression in blood

Application of TDA to blood transcriptomes of participants from the same U-BIOPRED cohort (246 nonsmoking patients with severe asthma, 88 smoking patients with severe asthmas,

TABLE II. Canonical pathways associated with T_H17 biology and host defense

	FDR *(q)*, Benjamini-Hochberg	*P** value, Fisher exact test	Ratio	Molecules
Canonical pathways associated with T_H17 biology				
Role of IL-17A in psoriasis	3.6E-04	3.5E-06	0.46	S100A8, S100A9, CCL20, DEFB4A/DEFB4B, CXCL3, CXCL8
IL-17A signaling in gastric cells	2.3E-02	1.9E-03	0.20	CXCL11, FOS, CXCL10, CCL20, CXCL8
Differential regulation of cytokine production in macrophages and T_H cells by IL-17A and IL-17F	4.0E-02	3.8E-03	0.22	IL1B, CSF3, CCL4, IL6
Differential regulation of cytokine production in intestinal epithelial cells by IL-17A and IL-17F	8.7E-02	9.3E-03	0.17	IL1B, DEFB4A/DEFB4B, CSF3, CCL4
Role of IL-17F in patients with allergic inflammatory airway diseases	1.4E-01	1.7E-02	0.12	IL1B, CXCL10, CCL4, IL6, CXCL8
Canonical pathways associated with host defense				
TREM1 signaling	8.1E-05	2.2E-07	0.20	TLR5, TLR7, MYD88, IL1B, IL6, CXCL8, TLR8, FCGR2B, CASP5, TREM1, DEFB4A/DEFB4B, CXCL3, ICAM1, TLR2
Toll-like receptor signaling	8.1E-05	3.9E-07	0.19	TLR5, TLR7, MYD88, IL1B, CD14, IRAK3, FOS, TLR8, LY96, IL1RN, TNFAIP3, TRAF4, TLR2, IL33
Communication between innate and adaptive immune cells	6.5E-04	9.3E-06	0.16	TLR5, TNFSF13B, TLR7, IL1B, CXCL10, FCER1G, IL6, CXCL8, TLR8, IL1RN, CCL4, TLR2, IL33
Interferon signaling	1.7E-03	4.1E-05	0.22	IFITM1, IFNGR2, IFIT3, IFITM2, MX1, PIAS1, TAP1, TYK2
iNOS signaling	1.6E-02	9.3E-04	0.16	FOS, LY96, MYD88, CD14, IFNGR2, TYK2, IRAK3
Role of pattern recognition receptors in recognition of bacteria and viruses	1.7E-02	1.1E-03	0.10	TLR5, TLR7, MYD88, IL1B, IL6, C3AR1, CXCL8, TLR8, C1QC, IRF7, OAS3, TLR2, PIK3C2G
Inflammasome pathway	6.8E-02	6.8E-03	0.19	MYD88, IL1B, CASP5, CXCL8

FDR, False detection rate; *iNOS*, inducible nitric oxide synthase.
*Significance indicates the probability of association of molecules from the data set with the canonical pathway by means of random chance alone. The 797-DEG list was used as input.

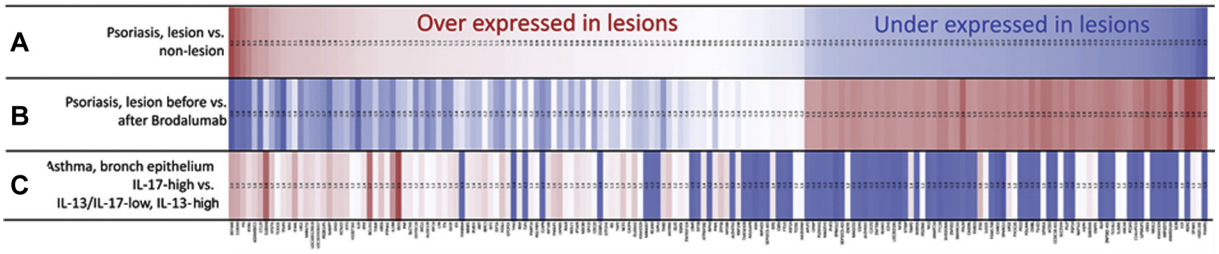

FIG 2. Fold change values (color coded) for 170 genes from 3 separate differential expression analyses by using transcriptomics data from skin of patients with psoriasis, lesion versus nonlesion **(A)**[22]; skin from patients with psoriasis, lesion before versus after brodalumab treatment **(B)**[22]; and asthmatic bronchial epithelial cells, IL-17–high versus IL-13/IL-17–low asthma and IL-13-high asthma in the current study **(C)**. Red and blue colors represent overexpression and underexpression, respectively.

77 nonsmoking patients with mild-to-moderate asthma, and 87 healthy nonsmokers) identified 9 clusters derived from transcriptomic data in whole blood (BCs): BC1, composed of patients with severe asthma (10.44% of total cohort), was enriched for *IL17A*, *IL21*, *IL22*, and *TGFB* transcripts (Fig 5, *A*) but was also enriched for *IL5*. Two other clusters, BC2 and BC9, were equally enriched for *IL5* and *IL13* transcripts and serum IL-13 levels. Colocalization of blood gene expression with the 3 epithelial clusters (Fig 5, *B*) showed no overlap between blood and airway IL-17–high and IL-13–high gene expression, with only 2 asthmatic patients present in the bronchial epithelium–based IL-17–high group and BC1.

Asthmatic patients in BC1 (Fig 5, *A*) had lower FEV_1 (72.21% ± 24.64% of predicted value vs 101.83% ± 12.99% of predicted value, $P = 1.93E-11$) and higher F_{ENO} values (29.81 ± 22.04 vs 21.72 ± 13.97 ppb, $P = .02$), age

TABLE III. Demographic and clinical characteristics of identified clusters

	Groups			Unadjusted *P* value		
	IL-17 high	IL-13/IL-17 low	IL-13- high	IL-17 high vs IL-13/IL-17 low	IL-17 high vs IL-13 high	IL-13 high vs IL-13/IL-17 low
Study participants	22/91 (24.2)	60/91 (85.9)	9/91 (9.9)			
Age (y)	44.8 ± 3.2	45.6 ± 1.9	43.2 ± 5.3	.8	.7	.7
Sex, female/male	8/14	38/22	5/4	.029	.326	.653
Severe asthma	13/22	32/60	8/9	.64	.11	.44
BMI (kg/m^2)	25.9 ± 1	29.7 ± 0.8	28.5 ± 4.6	.006	.16	.62
FEV_1 % predicted	79.6 ± 4.6	84.3 ± 2.7	73 ± 8.1	.33	.49	.16
Exacerbations in the past year	2 ± 0.4	1.2 ± 0.2	2.7 ± 0.96	.124	.608	.127
Two or more exacerbations in the past year	8/21 (38)	9/60 (15)	4/9 (44.4)	.025	.754	.035
Never smokers	15/22 (68.1)	53/60 (88.3)	9/9 (100)	.0317	.054	.280
Ex-smokers	7/22 (31.8)	7/60 (11.7)	0/9 (0)	.0317	.054	.280
Smoking history (pack-years)	2.7 ± 0.69	1.4 ± 0.56	0	.179	NA	NA
Atopic	19/21 (90)	41/52 (79)	7/9 (78)	.4	.7	.7
Age of onset (% below age <12 y)	12/22	27/57	2/8	.567	.151	.233
Allergic rhinitis	13/21 (61.9)	31/53 (58.5)	4/9 (44.4)	.787	.561	.651
Nonallergic rhinitis	3/19 (15.7)	8/53 (15.1)	3/9 (33.3)	.942	.291	.185
Eczema	12/21 (57.1)	21/55 (38.2)	3/9 (33.3)	.136	.232	.781
Nasal polyp surgery	9/21 (42.9)	8/55 (14.5)	0/9 (0)	.008	.018	.22
GORD diagnosed	6/21 (28.6)	28/55 (50.2)	2/9 (22.2)	.08	.72	.110
Regular treatment, ICS	22/22 (100)	58/60 (96.7)	9/9 (100)	.386	NA*	.578
Regular treatment, OCS	7/22 (31.8)	12/57 (21.1)	2/8 (25)	.31	.7	.8
Regular treatment, omalizumab	2/21 (9.5)	2/56 (3.6)	0/6 (0)	.295	.397	.611
Regular treatment, antibiotics including macrolides	6/22 (27.3)	5/57 (8.8)	0/7 (0)	.032	.12	.41
Regular treatment, macrolides	4/22 (18.2)	4/60 (7)	0/9 (0)	.119	.170	.208
Regular treatment, LT modifier	8/22 (36.4)	16/57 (28.1)	4/8 (50)	.47	.5	.21
Regular treatment, xanthines	1/21 (4.8)	5/56 (8.9)	1/8 (12.5)	.746	.424	.746
FENO (ppb)	32 (16-46)	40.9 (18.5-55)	59.9 (37.6-69.8)	.356	.097	.172
Blood eosinophils (× 10E-03/μL)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.5 (0.3-0.8)	.8	.028	.012
Blood eosinophils (%)	3.6 (1.9-5.1)	3.7 (1.8-4.4)	7.9 (3.7-11.1)	.7	.025	.012
Blood neutrophils (× 10E-03/μL)	4.7 (2.9-5.7)	4.2 (3.1-5.1)	3.9 (1.9-5.8)	.892	.433	.649
Blood neutrophils (%)	62.1 (53.9-70.9)	60.2 (53.4-67.8)	53.2 (42.7-58)	.675	.555	.748
Sputum eosinophils (%)†	6.25 (0.5-6.2 [n = 12])	3.2 (0.1-4.4 [n = 27])	49.3 (45-53.6 [n = 2])	.35	.0283	.0193
Sputum neutrophils (%)†	63.7 (52.2-77 [n = 12])	48.7 (33.3-59.8 [n = 27])	38.6 (31.7-45.4 [n = 2])	.045	.144	.49

Data are presented as numbers of participants assessed, means ± SEs, percentages, n/N values (percentages), or medians (interquartile ranges [q1-q3]).
GORD, Gastro-oesophageal reflux disease; *LT*, leukotriene; *OCS*, oral corticosteroid.
*All asthmatic patients were receiving ICSs, and therefore no statistical analysis was done *(NA)*.
†Not all participants produced good quality sputum, and therefore numbers of quality control–passed samples are shown in parentheses for each group.

(51.44 ± 14.73 vs 39.37 ± 13.71 years, P = 5.66E-06), blood neutrophil counts (5.63 vs 3.44 ± 1.65 × 10^9 L, P = 4.97E-08), blood eosinophil counts (0.31 ± 0.3 vs 0.14 ± 0.11 × 10^9 L, P = 3.12E-04), sputum neutrophil percentages (30.18% ± 36.16% vs 15.34% ± 23.57%, P = 9.92E-03), and eosinophil percentages (1.67% ± 5.16% vs 0.09% ± 0.28%, P = .03) when compared with healthy control subjects but was not different in terms of sputum eosinophil counts compared with the rest of the cohort.

BC9 (9.43% of the total cohort; Fig 5, *A*), with high IL-13 but not increased IL-17 expression, a high atopy rate (80% compared with 65% for BC1 and 37% for healthy participants), lower FEV_1 (71.69% ± 24% vs 101.83% ± 12.99% of predicted value, P = 4.46E-11), age (50.8 ± 15.58 vs 39.37 ± 13.71 years, P = 6.08E-05), and greater blood eosinophil counts (0.35 ± 0.33 vs 0.14 ± 0.11 × 10^9 L, P = 1.24E-04), and smoking pack-years (1.65 ± 1.48 vs 0.38 ± 1.15, P = .01) compared with healthy control subjects. The other IL-13–high cluster, BC2 (11.84% of total cohort), was characterized by lower FEV_1 (66.04% ± 20.76% vs 101.83% ± 12.99% of predicted value, P = 5.37E-13), greater blood neutrophil counts (6.78 ± 2.94 vs 3.44 ± 1.65 × 10^9 L, P = 5.37E-13), age (53.03 ± 14.44 vs 39.37 ± 13.71 years, P = 3.31E-06), and sputum eosinophil counts (6.37 ± 14.89 vs 0.09 ± 0.28, P = 6.19E-04) but notably no difference in atopy or blood periostin values compared with healthy control subjects.

Associations between blood and urine biomarkers and the IL-17–high phenotype

An exploratory search of readily available U-BIOPRED blood and urine biomarkers associated with the IL-17–high phenotype by using logistic regression identified a number of potential blood transcripts, but when false detection rate corrected, none were statistically significant (see Table E5 in this article's Online Repository at www.jacionline.org). However, urinary 11 dehydrothromboxane B2, a degradation of product of thromboxane B2, was positively associated with the IL-17–high phenotype

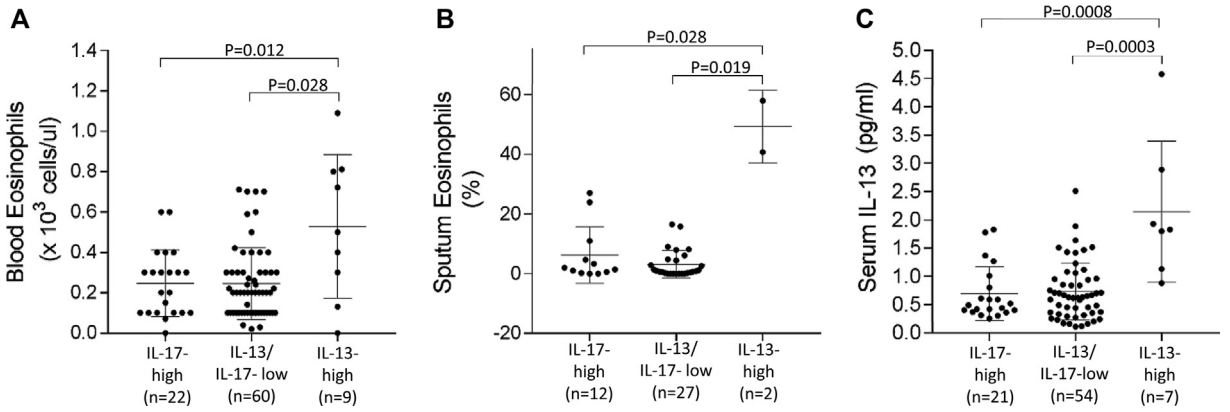

FIG 3. Blood and sputum inflammatory biomarkers distinguishing IL-17–high and IL-13–high clusters. Counts of blood eosinophils **(A)** and sputum eosinophils **(B)** and serum IL-13 concentrations **(C)** are greater in the IL-13–high group compared with the IL-17–high and IL-13/IL-17–low groups. *P* values (Kruskal-Wallis test) are indicated for pairwise comparisons. Scatter plots indicate values of the median and 25th and 75th percentiles.

($z = 2.655$, $P = .008$, and false detection rate $q = 0.56$; see Table E6 in this article's Online Repository at www.jacionline.org). Previous studies have shown expression of this biomarker to be increased in both spontaneous and allergen challenge–induced asthma exacerbations.[27,28]

Decreased microbial diversity in patients with an IL-17–high phenotype

We hypothesized that microbial diversity would be lower in patients with the IL-17–high phenotype, which is in keeping with reports in patients with neutrophilic asthma.[29] Sputum microbiome data were available from 24% of the whole adult cohort but only a few participants in this analysis (6/22 [27%] in the IL-17–high group, 15/60 [25%] in the IL-13/IL-17–low group, and 1/10 [11%] in the IL-13–high group). Both 16S- and next-generation sequencing based metagenomics analysis–derived data were retrieved and analyzed in respect to potential differences in the microbiota among the 3 phenotypes, and differential analysis was performed by using metagenomics data. The Shannon α-diversity index was lower in those with the IL-17 phenotype compared with the rest of the cohort ($P = .054$), with a trend toward reduction when compared with patients with IL-13/IL-17–low asthma ($P = .2$, see Fig E2 in this article's Online Repository at www.jacionline.org). Patients with IL-17–high asthma showed the lowest diversity index in both patients with severe and those with mild-to-moderate asthma (see Fig E2). Sputum neutrophil counts correlated inversely with the Shannon α-diversity index in the IL-17–high group ($R = -0.76$, $P = .0825$), more strongly than in any of the other separate groups (data not shown).

Screening of the complete list of operational taxonomic unit abundance data showed no OTUs with clear differences between the phenotypes. Analyzing the abundance of *a priori*–selected OTUs related to bacterial exacerbation showed lower abundance of *Haemophilus influenzae* ($P = .039$) in the IL-17–high group when compared with all other asthmatic patients (data not shown). *Moraxella* species were poorly represented and did not differ between groups (data not shown).

DISCUSSION

Using a gene expression signature for IL-17–induced bronchial epithelial activation,[12] we identified a group of asthmatic patients with an IL-17–high phenotype, comprising about a quarter of patients studied and consisting of similar proportions of patients with mild-to-moderate and severe asthma. A high percentage of these had more than 2 exacerbations in the year preceding the study and surgery for nasal polyps and used antibiotics regularly. Their pathobiology was characterized by airway neutrophilia, which is consistent with the described role of IL-17 in patients with neutrophilic diseases and with IL-17 responses to mucosal bacterial infections, with additional features being mucosal T-cell infiltration and low numbers of mast cells.

Using the epithelial gene signature identified by Choy et al[12] as an indirect marker of IL-17 pathway activation, we have shown that patients with upregulated IL-17 immunity exhibit differential expression of several genes previously associated with IL-17 pathway activation. Many of these overlapped with DEGs in psoriatic lesions and are altered when IL-17 signaling is blocked by mAb targeting of the IL-17 receptor.[25] Together, these findings give confidence to our approach to identifying patients with the IL-17–high phenotype.

When epithelial DEGs from patients with T17-high asthma were matched against the IPA database, the canonical pathway of psoriasis appeared as the disease with the greatest overlap and significance. High overlap was also seen by using disease and function enrichment analysis. Because the U-BIOPRED clinical assessment questionnaire did not have specific questions about a past or present diagnosis of psoriasis, we are unable to make any conclusions about the comorbidity of asthma and psoriasis in the current study, although epidemiologic studies done by others have pointed to an association between the 2 diseases in both children and adults.[30-32] Therefore we speculate that mechanisms similar to those in patients with psoriasis might be implicated in the pathobiology of asthmatic patients with the IL-17–high phenotype, in which bronchial epithelial dysfunction and inflammatory mechanisms would be major drivers defining the clinical outcome. In further support of this link between the 2 diseases, increased levels of urinary 11 dehydro-thromboxane B2 were

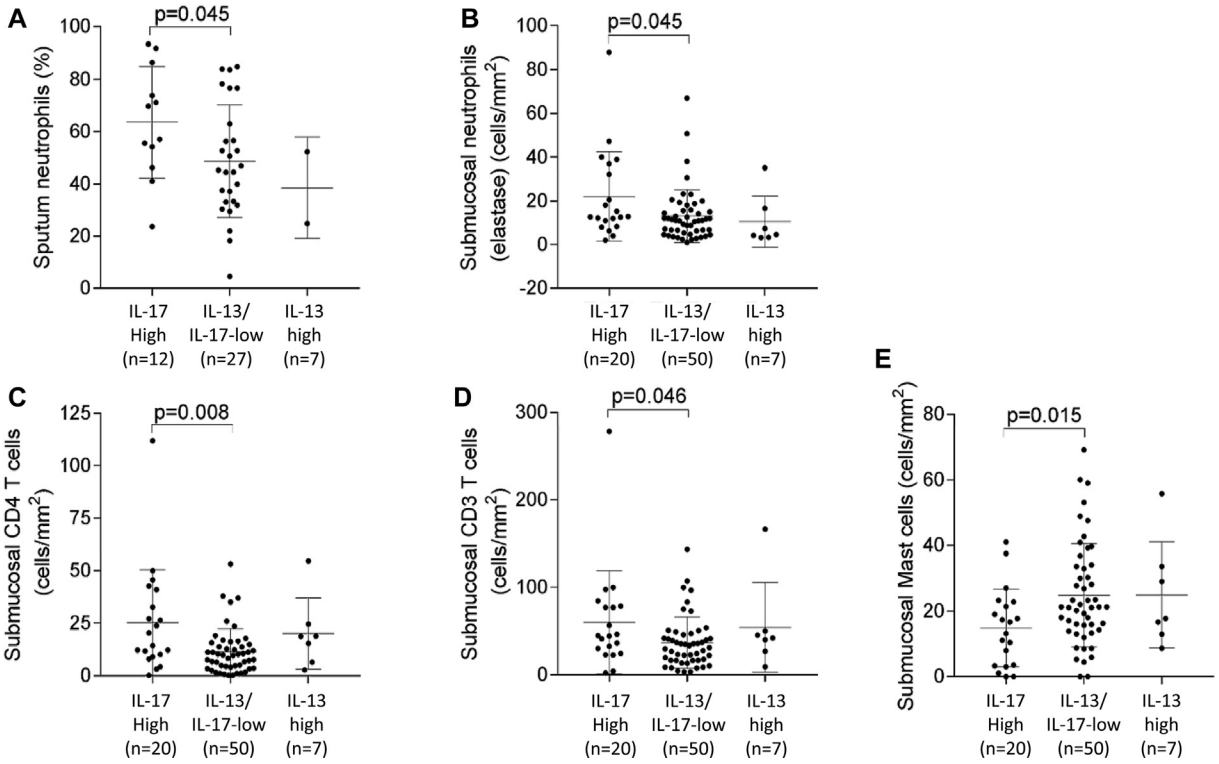

FIG 4. Inflammatory cell counts distinguishing IL-17–high and IL-13–high clusters. **A-D,** The percentage of neutrophils in sputum (Fig 4, *A*), the number of neutrophils in the submucosa (Fig 4, *B*), and the number of infiltrated $CD4^+$ (Fig 4, *C*) and $CD3^+$ (Fig 4, *D*) T cells are greater in the IL-17–high group compared with the IL-13/IL-17–low group. **E,** Numbers of infiltrated mast cells are lower in the IL-17–high group compared with those in the IL-13/IL-17–low group. *P* values (Kruskal-Wallis test) are indicated for pairwise comparisons.

strongly associated with the IL-17–high phenotype. This breakdown product of thromboxane 2 was recently shown in a psoriasis model to facilitate IL-17 production by $Vg4^+$ γδ T cells, suggesting a pathogenetic role.[33]

Patients with the IL-17 phenotype had reduced expression of several genes regulating epithelial tight junctions and mucosal barrier mechanisms, a novel finding suggesting that epithelial leakage is a specific feature of IL-17 asthma. IL-17 and in particular IL-22, belonging to IL-17 pathway cytokines, are known to support epithelial homeostasis and antimicrobial responses in the healthy gut and lung mucosa.[34] Decreased microbial diversity, an indicator of dysbiosis, was also a feature of IL-17–high asthma, which, together with enhanced IL-17 activation, could be implicated in the observed dysregulated epithelial integrity and susceptibility to infections and exacerbations seen in these patients. Increased expression of the antimicrobial peptide β-defensin 2 further suggests that microbial alterations might be associated with IL-17 activation. Microbiome analyses were available in a small subgroup of patients with IL-17–high asthma, making it impossible to draw possible conclusions about the candidate microbial trigger of IL-17 immunity.

A study in a murine asthma model showing that LPS induces a switch from eosinophilic to neutrophilic inflammation with associated decreases in levels of T2 cytokines and increases in IL-17 levels and T_H17 cell counts has suggested that bacteria can drive IL-17 immunity.[35] Almost a third of patients with IL-17–high and none of the patients with IL-13–high asthma were ex-smokers, suggesting that past cigarette smoke exposure might have influenced the development of the phenotype with altered lung microbiota and neutrophilic airway inflammation. In support of this concept, evidence points to the IL-17 pathway being upregulated in patients with chronic obstructive pulmonary disease, a disease characterized by neutrophilic inflammation and caused primarily by smoking.[36] A recent study of asthmatic smokers, combining an *in vivo* analysis of IL-17A expression and exposure of epithelial cells *ex vivo* to cigarette smoke extract, has supported that smoking induces neutrophilia through IL-17 induction.[37] Furthermore, smoking is known to contribute to alterations of microbiota and epithelial barrier function. A mouse model of chronic obstructive pulmonary disease has shown that airways neutrophilia, exacerbated by nontypeable *Haemophilus* influenza infection and associated with increased IL-17 production, is inhibited by anti–IL-17A antibody without increasing the microbial burden.[38]

It has been suggested that impaired responses to ICSs are associated with IL-17 immunity and/or that ICS downregulation of T2 immunity promotes IL-17 immunity in asthmatic patients.[39] Our data do not directly support the former concept but suggest that ICSs can enable IL-17 immunity to express itself. Using asthma severity as a proxy for a poor corticosteroid response, we have found an equal distribution of patients with IL-17–high asthma among those with mild/moderate/severe disease, which

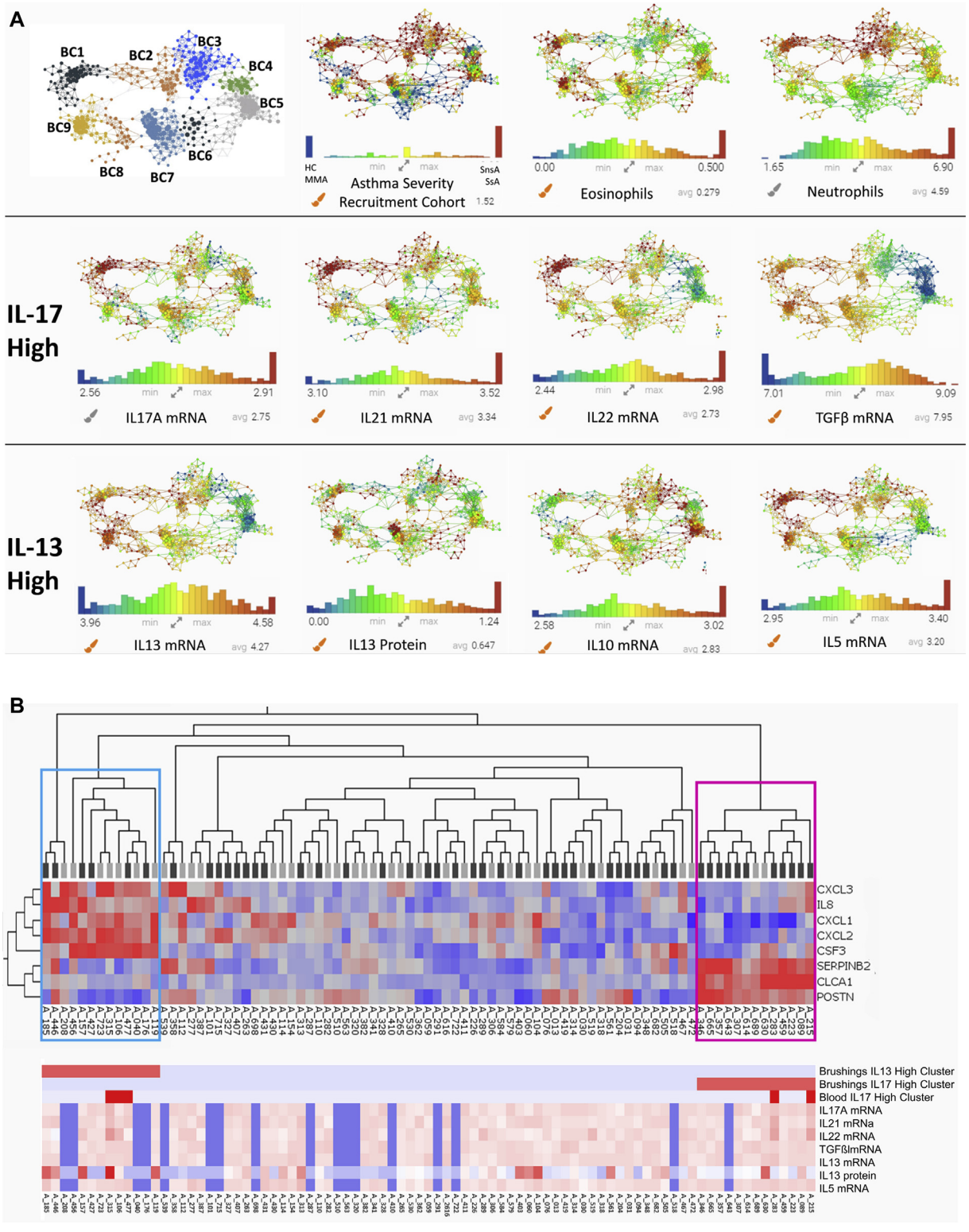

FIG 5. Comparison with IL-13–high and IL-17–high BCs (see the second figure in Fig 5, *A*) identified in blood. **A,** TDA networks of blood transcriptomics data with heat map coloring for key asthma-related clinical variables and IL-17– and IL-13–associated gene expression. **B,** Heat map of the expression of selected IL-17 and IL-13 in blood aligned to IL-17 and IL-13 bronchial brushing cluster assignments. A total of 9 blood-based clusters, 7 of which were validated by using machine learning (receiver operating characteristic area under the curve of logistic regression models, >0.70). Scales (colors) in Fig 5, *A*, indicate relative levels of expression of the gene in question in blood. In Fig 5, *B*, colors in rows 1 to 3 indicate membership of the IL-17– and IL-13–high clusters. In the other rows colors indicate relative levels of expression of the gene in question in blood.

does not support the association of the IL-17 phenotype and an impaired treatment response to ICSs. Although the frequency of patients with IL-17–high asthma was 25% in our cohort, we found only 1 patient with IL-17–high asthma in the steroid-free cohort of Woodruff et al.[16] This suggests that ICS treatment can be associated with development of IL-17 immunity in asthmatic patients, possibly because of effective suppression of T2 immunity in the lungs that allows an IL-17 phenotype to emerge. Indeed, both our study and that of Choy et al[12] suggest no coexistence of IL-13 and IL-17 pathway activation in asthmatic lungs, at least when epithelial responses are used as a marker. In contrast, our analysis of blood showed upregulation of both IL-13 and IL-17 gene signatures in the same subjects. Together with an earlier report of increased blood T cells secreting both T2 and T17 cytokines in asthmatic patients,[40] this suggests that T2 and T17 activation can coexist, at least in blood T cells.

A previous study by Hinks et al[20] analyzing cytokine profiles in airway secretions and airway cells of 60 patients with mild-to-severe asthma did not show differences in the frequencies of bronchoalveolar lavage fluid T_H17 cells or IL-17$^+$ γδ T cells. The source of IL-17 in the lungs could be T cells, lung γδ T cells, or, according to a recent study, also eosinophils.[41] Together with our finding of coexpression of IL-5 and IL-17 in peripheral blood, this suggests the need to revisit the concept of eosinophilic asthma being purely a T2 disease. This might also be needed in nasal polyps in which upregulation of IL-17 immunity polyps has been reported in association with blood eosinophilia.[42] Indeed, and in contrast to our study, Choy et al[12] found eosinophilia in asthmatic patients with an IL-17–high gene signature. Thus it cannot be excluded that some patients with IL-17–high asthma could respond to anti–IL-5 treatments that target IL-5 and eosinophils.

This study has some limitations, such as the limited availability of sputum samples in patients with the IL-13–high phenotype for comparison of granulocyte counts with the IL-17–high phenotype, as well as limited analysis of the microbiome; all of this will require further studies. We also recognize the observational nature of our study but emphasize its importance for future mechanistic studies and clinical trials targeting IL-17. Nevertheless, together with Choy et al,[12] we show that the IL-17 phenotype can be identified reliably, with clinical and immunologic features that define a distinct disease phenotype, and because they constituted a quarter of the U-BIOPRED patients, we propose that there is a sufficient case for developing drugs for this phenotype. Past attempts to inhibit IL-17 signaling with the anti–IL-17 receptor A antibody brodalumab have failed in respect of the primary outcome while showing possible improvement in asthma symptoms (Asthma Control Questionnaire score) in a select population with highly reversible airway obstruction.[43] Similar to the approach taken for biologics targeting T2-high asthma, effective IL-17 pathway blocking would require patient stratification, and urine dehydro-thromboxane B2 in patients with T17-high asthma offers a potential biomarker that could be used, possibly in combination with high airway reversibility.[43]

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Clinical implications: This study points to shared mechanisms between asthma and psoriasis, with implications for treatments targeting IL-17–driven mechanisms.

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